FORMULATION, DEVELOPMENT AND EVALUATION OF BRAIN TARGETED STARCH NANOPARTICLES OF ANTICONVULSANT AGENT

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Introduction

Neurological disorders encompass a wide range of conditions that impact the nervous system, comprising the brain, spinal cord, and peripheral nerves. These ailments pose substantial challenges to healthcare systems worldwide due to their multifaceted origins, intricate mechanisms, and profound effects on individual health. Grasping the root causes of neurological diseases is essential for developing better diagnostic methods, tailoring treatments, and ultimately enhancing patient results.

The varied clinical presentations, distinct progressions, and treatment responses characterize the manifestation of these conditions. The wide array of neurological issues underscores the intricate nature of the human nervous system. These encompass a spectrum from neuropsychiatric disorders such as depression and schizophrenia to epileptic syndromes, multiple sclerosis, and neurodegenerative ailments like Alzheimer's and Parkinson's diseases. Factors like aging, environmental influences, genetic predispositions, and lifestyle choices contribute to the increasing prevalence of these disorders globally. Consequently, there is a pressing need for extensive research endeavours aimed at deciphering the complexities of these conditions [1].

Recent advancements in computational modelling, molecular biology, genetics, and neuroimaging have transformed our comprehension of neurological conditions. Neuroimaging techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetic resonance imaging (MRI), furnish crucial insights into the structural and functional alterations in the brain associated with various neurological disorders. Molecular and genetic investigations have identified significant genes, pathways, and biomarkers implicated in disease etiology, presenting promising targets for therapeutic interventions and personalized medicine strategies. Artificial intelligence and computational modelling hold considerable promise for enhancing diagnostic accuracy, treatment optimization, and disease progression assessment.

Despite considerable progress, several challenges remain in the field of neurological disorders research. The diversity of these conditions, limited understanding of disease mechanisms, and the barrier posed by the blood-brain barrier create obstacles to diagnosis and treatment efforts. Additionally, current treatments frequently focus on symptom management rather than targeting the underlying causes of neurological disorders. This highlights the urgent requirement for innovative research strategies to identify new therapeutic targets, develop treatments that modify the course of the disease, and improve patient care.

EPILEPSY

Epilepsy represents a considerable global public health issue, impacting millions of individuals across diverse demographics and geographical locations. According to the World Health Organization (WHO), epilepsy is among the most prevalent neurological disorders worldwide, affecting approximately 50 million people [2]. This high prevalence underscores the significant burden it imposes on affected individuals, families, and healthcare systems worldwide.

The influence of epilepsy transcends borders and socioeconomic disparities, affecting individuals of all ages and backgrounds. While the disorder can arise at any life stage, it frequently emerges during childhood or early adulthood, with the highest incidence occurring within the first year of life and among individuals aged over 65. This wide age range underscores the pervasive nature of epilepsy and its potential to disrupt lives at various developmental stages and during aging.

The burden of epilepsy extends beyond the physical manifestations of seizures to encompass a variety of psychosocial and economic hurdles. Individuals with epilepsy may encounter substantial obstacles to education, employment, and social engagement due to stigma, discrimination, and misconceptions surrounding the condition. Epilepsy is linked to an elevated risk of comorbidities, including cognitive deficits, mental health disorders like anxiety and depression, and sleep disturbances, further impacting overall quality of life.

Epilepsy is also associated with heightened mortality rates, as individuals affected by the condition confront an elevated risk of premature death compared to the general populace. Sudden unexpected death in epilepsy (SUDEP) is an especially concerning occurrence, responsible for a notable portion of epilepsy-related fatalities. Despite its prevalence, SUDEP remains inadequately comprehended, highlighting the critical necessity for enhanced seizure management and healthcare access [3].

Despite the existence of efficacious treatments, a substantial treatment gap persists for epilepsy on a global scale, particularly in low- and middle-income nations. Limited availability of healthcare services, diagnostic resources, and anticonvulsant medications contributes to disparities in epilepsy care, intensifying the burden of the disorder among underserved communities. Obstacles to diagnosis and treatment, such as insufficient awareness, societal stigma, and scarcities of adequately trained healthcare personnel, further exacerbate these hurdles.

Epilepsy is a chronic neurological condition characterized by recurrent, unprovoked seizures resulting from abnormal electrical discharges in the brain. The nature of seizures can vary depending on the specific brain region affected and the underlying cause of the disorder. Epilepsy can affect individuals across all

age groups and demographics, with the severity and impact on daily functioning varying significantly from person to person.

Classification of Epilepsy [3]

Epilepsy is typically categorized into two primary types based on the origin and characteristics of seizures:

1. Focal Epilepsy: Seizures originate in a particular area of the brain and may either remain localized or spread to adjacent regions. Symptoms of focal seizures are contingent upon the specific brain area involved and may encompass alterations in sensation, vision, hearing, taste, or motor function.

2. Generalized Epilepsy: Seizures encompass both cerebral hemispheres from their onset, often resulting in a loss of consciousness.

Causes of Epilepsy

Epilepsy can stem from hereditary factors or specific genetic mutations in some instances. Structural abnormalities in the brain, such as tumors, malformations, or scarring resulting from injury or surgery, can also cause epilepsy. Traumatic brain injuries, infections like meningitis or encephalitis, and complications during pregnancy or birth (such as oxygen deprivation or low birth weight) can elevate the likelihood of developing epilepsy later in life. Certain metabolic imbalances or conditions, such as hypoglycaemia or mitochondrial disorders, may also trigger seizures. In some cases, the precise cause of epilepsy remains elusive, a circumstance referred to as idiopathic or cryptogenic epilepsy [4].

Impact on Patients' Lives

Individuals living with epilepsy may endure injuries from falls or accidents during seizures, alongside other physical health issues associated with the condition. Epilepsy can significantly affect mental well-being, precipitating anxiety, depression, and other mood disorders owing to the unpredictable nature of seizures. Social stigma linked to epilepsy can engender discrimination and social isolation, impacting interpersonal relationships and social interactions. Seizures and the apprehension of experiencing them can diminish a patient's quality of life, curtailing their capacity to work, drive, and engage in daily activities. Medications employed to manage epilepsy can elicit side effects such as drowsiness, dizziness, and cognitive impairments, further impinging on a patient's daily functioning. Epilepsy can impede educational and vocational prospects due to the unpredictability of seizures and potential medication-related adverse effects [5].

ANTIEPILEPTIC MEDICATIONS

Medications utilized in the treatment of epilepsy, commonly referred to as antiepileptic drugs (AEDs) or anticonvulsants, play a pivotal role in seizure management and enhancing the well-being of individuals grappling with epilepsy. These pharmacological agents function by stabilizing the electrical activity of neurons within the brain, thereby thwarting the abnormal surges of electrical impulses that precipitate seizures [4].

Mechanisms of Action

1. Sodium Channel Blockade: Numerous AEDs exert their effects by impeding voltage-gated sodium channels, thereby diminishing neuronal excitability and impeding the propagation of aberrant electrical activity.

2. Calcium Channel Inhibition: Certain AEDs hinder calcium channels, which are integral to neurotransmitter release and neuronal excitability regulation.

3. Augmentation of GABA Activity: Gamma-aminobutyric acid (GABA) serves as an inhibitory neurotransmitter pivotal in modulating neuronal activity. Specific AEDs heighten GABAergic transmission, curbing neuronal excitability and thwarting seizure occurrence.

4. Antagonism of Glutamate Receptors: Glutamate stands as the primary excitatory neurotransmitter in the brain. AEDs that antagonize glutamate receptors mitigate neuronal excitability, thus forestalling seizure onset.

Types of Epilepsy Medications

1. First-Line AEDs: These drugs serve as primary treatment options for epilepsy and exhibit broad efficacy against various seizure types. Examples encompass:

    - Carbamazepine
    - Valproic acid (valproate)
    - Lamotrigine
    - Levetiracetam
    - Oxcarbazepine

2. Second-Line AEDs: When initial-line medications prove ineffective or poorly tolerated, secondary-line AEDs may be prescribed. These drugs may possess narrower spectra of activity or target specific seizure types. Instances include:

- Topiramate
- Gabapentin
- Pregabalin
- Zonisamide
- Lacosamide

3. Newer AEDs: Recent years have witnessed the introduction of several novel AEDs, offering alternative therapeutic avenues with potentially enhanced tolerability and reduced drug interactions.

- Brivaracetam
- Eslicarbazepine acetate
- Perampanel
- Rufinamide

Treatment Considerations

- Tailored Therapy: AED selection hinges on variables like seizure categorization, patient age, gender, coexisting conditions, potential drug interactions, and patient preferences.
- Monotherapy vs. Combination Therapy: While monotherapy suffices for many individuals in achieving seizure management, others may necessitate polytherapy, employing multiple medications for optimal seizure control.
- Dosage Adjustment: AEDs typically commence at low dosages, with gradual titration upward to mitigate side effects and attain therapeutic blood levels.
- Vigilant Monitoring: Regular monitoring of seizure frequency, blood medication levels, and potential adverse reactions is imperative to ensure treatment efficacy.
- Safety Precautions: AEDs can elicit various side effects, encompassing drowsiness, dizziness, weight fluctuations, cognitive deficits, and mood alterations. Hence, healthcare practitioners must meticulously weigh the risks and benefits of each medication for individual patients.

Challenges [5]

(a) Drug Resistance

Some individuals may develop resistance to epilepsy drugs, resulting in persistent seizures despite treatment with multiple AEDs. Ongoing research is dedicated to exploring novel treatment approaches and understanding the mechanisms underlying drug resistance.

(b) Side Effects

The mitigation of side effects and enhancement of AED tolerability represent ongoing challenges in epilepsy management. There is a continual need for research into new medications characterized by improved safety profiles.

(c) Access to Care

Disparities in access to epilepsy care, particularly prevalent in low- and middle-income countries, pose a significant obstacle to achieving optimal treatment outcomes. Initiatives aimed at enhancing access to diagnostic resources, medications, and specialized epilepsy care are imperative in addressing this issue.

NANOPARTICLES & STARCH NANOPARTICLES

Nanoparticles are particles sized in the nanometer range, typically from 1 to 100 nanometers, and can be fashioned from various materials such as metals, polymers, ceramics, and biological substances. Their unique physical, chemical, and biological attributes, distinct from bulk materials, render them highly appealing for diverse applications spanning medicine, electronics, energy, and environmental cleanup.

In pharmaceutical contexts, starch nanoparticles are particularly noteworthy for their distinctive traits and versatile utility in drug delivery and therapeutics. Derived from starch, a natural polysaccharide, these nanoparticles offer numerous advantages conducive to various pharmaceutical formulations and biomedical uses [6].

A primary merit of pharmaceutical starch nanoparticles lies in their biocompatibility and biodegradability. Originating from a natural source, starch nanoparticles are devoid of toxicity and well-received by the body, thus proving ideal for drug delivery systems and biomedical applications without instigating significant adverse reactions or immune responses. This inherent biocompatibility assures the safety of starch nanoparticles in human applications, effectively mitigating the risk of toxicity or undesirable effects typically associated with synthetic nanoparticle counterparts.

Another significant attribute of pharmaceutical starch nanoparticles is their efficacy in encapsulating and delivering therapeutic substances. Starch nanoparticles can act as carriers for drugs, proteins, nucleic acids, and other bioactive compounds, shielding them from degradation and facilitating controlled release at specific sites of action. Through encapsulation within starch nanoparticles, drugs can experience

enhanced stability, solubility, and bioavailability, alongside the potential for targeted delivery to precise tissues or cells within the body. This targeted delivery approach amplifies the therapeutic effectiveness of drugs while minimizing unintended effects and decreasing systemic toxicity [7].

Starch nanoparticles offer adaptability in formulation and engineering, enabling tailoring to meet specific application demands. Starch nanoparticles are readily modifiable or functionalizable with targeting ligands, surface coatings, or other molecules to augment their specificity, stability, and functionality. This flexibility empowers the creation of bespoke drug delivery systems with refined characteristics tailored for particular therapeutic applications, such as cancer treatment, infectious disease management, or regenerative medicine.

The utility of pharmaceutical starch nanoparticles spans a broad spectrum of biomedical applications, encompassing drug delivery, diagnostic imaging, tissue engineering, and regenerative medicine. In drug delivery, starch nanoparticles can be harnessed to encapsulate and transport a diverse array of therapeutic agents—including small molecule drugs, biologics, and nucleic acids—for addressing various diseases and disorders. In diagnostic imaging, starch nanoparticles can be functionalized with contrast agents to heighten visualization of anatomical structures or pathological anomalies in medical imaging modalities like magnetic resonance imaging (MRI), computed tomography (CT), or ultrasound. Furthermore, in tissue engineering and regenerative medicine, starch nanoparticles can function as scaffolds or vehicles for cell growth factors, fostering tissue regeneration and restoration in applications such as wound healing, bone reconstruction, and organ transplantation [8].

Therefore, pharmaceutical starch nanoparticles emerge as a promising platform for drug delivery and biomedical applications, offering attributes like biocompatibility, versatility, and targeted delivery capabilities. Ongoing research and development in this domain are poised to unveil novel avenues for innovation and progress in the realm of medicine and healthcare.

Encapsulation efficiency

Encapsulation efficiency stands as a pivotal parameter in the advancement of pharmaceutical starch nanoparticles, as it directly impacts drug delivery efficacy and therapeutic outcomes. This metric denotes the ratio of drug molecules encapsulated within the nanoparticles relative to the total drug quantity utilized during formulation. Attaining high encapsulation efficiency is crucial for optimizing the therapeutic payload delivered to the target site while minimizing drug wastage and potential adverse effects.

Numerous factors influence the encapsulation efficiency of pharmaceutical starch nanoparticles, encompassing the properties of both the drug and the nanoparticles, along with formulation and processing

conditions. The physicochemical properties of the drug, including its solubility, molecular weight, and hydrophobicity, significantly dictate its encapsulation efficiency. Drugs with greater solubility and compatibility with the nanoparticle matrix are more likely to achieve efficient encapsulation, while those that are poorly soluble or hydrophobic may demonstrate lower encapsulation efficiency due to aggregation or precipitation phenomena [9].

Moreover, the attributes of the nanoparticles themselves—such as size, shape, surface charge, and composition—exert a notable influence on encapsulation efficiency. Smaller nanoparticles boasting a heightened surface area-to-volume ratio typically exhibit increased drug loading capacity and encapsulation efficiency compared to their larger counterparts. Additionally, surface modifications or functionalization of nanoparticles can augment drug loading and encapsulation by fostering interactions between drug molecules and the nanoparticle matrix.

The formulation and processing parameters applied during nanoparticle preparation are pivotal in determining encapsulation efficiency. Factors like solvent selection, nanoparticle synthesis method (e.g., nanoprecipitation, emulsification, or solvent evaporation), drug and polymer concentrations, and processing conditions (e.g., temperature, pH, and agitation) can all impact drug encapsulation efficiency. Optimization of these parameters is essential to achieve maximal drug loading and encapsulation while upholding nanoparticle stability and integrity.

Encapsulation efficiency measurement typically entails analytical techniques such as ultraviolet-visible (UV-Vis) spectroscopy, high-performance liquid chromatography (HPLC), or mass spectrometry. These methods involve quantifying the amount of drug encapsulated within the nanoparticles and comparing it to the total drug quantity used in the formulation process. Encapsulation efficiency is represented as a percentage, with higher values indicating superior efficiency in drug encapsulation [10].

High encapsulation efficiency is desirable in pharmaceutical starch nanoparticles to ensure adequate drug delivery to the target site, thereby optimizing therapeutic efficacy while minimizing adverse effects and drug wastage. Optimization of formulation parameters and characterization techniques is imperative for achieving high encapsulation efficiency and developing effective drug delivery systems based on starch nanoparticles. Continued research and innovation in nanoparticle technology are anticipated to further enhance drug encapsulation efficiency and broaden the applications of pharmaceutical starch nanoparticles in medicine and healthcare.

BRAIN TARGETED DELIVERY

Delivering drugs effectively to the brain is crucial in epilepsy management due to the distinctive hurdles presented by the blood-brain barrier (BBB) and the specific requisites for efficient seizure control. The BBB acts as a highly discerning semipermeable barrier, regulating the passage of molecules from the bloodstream into the brain to safeguard it from toxins and pathogens while maintaining equilibrium [11]. Nonetheless, the BBB also serves as a significant obstacle to delivering antiepileptic drugs (AEDs) to the brain, as many conventional drugs struggle to permeate this barrier effectively. Thus, achieving optimal drug concentrations at the brain's site of action while minimizing systemic exposure is imperative for maximizing therapeutic effectiveness and minimizing adverse reactions.

Epilepsy is typified by abnormal electrical activity in the brain, culminating in recurring seizures and associated neurological manifestations. Effectively managing epilepsy necessitates the administration of AEDs capable of curbing seizure activity and stabilizing neuronal excitability. However, attaining therapeutic drug levels in the brain poses challenges due to the limited permeability of the BBB to numerous AEDs, resulting in suboptimal drug concentrations and inadequate seizure management [12]. Consequently, there exists a pressing need for innovative drug delivery strategies capable of surmounting the BBB and specifically targeting AEDs to the brain.

Targeting drugs specifically to the brain presents a promising avenue for tackling the hurdles associated with delivering AEDs to the brain in epilepsy. These systems aim to augment drug delivery across the BBB and enhance drug distribution and retention within the brain tissue. A variety of approaches have been investigated to achieve brain targeting, encompassing nanoparticle-based drug carriers, prodrug formulations, receptor-mediated transport systems, and invasive techniques such as intracerebral implantation or direct infusion.

Among these strategies, nanoparticle-based drug delivery systems have emerged as particularly promising platforms for brain-targeted drug delivery in epilepsy. Nanoparticles can encapsulate AEDs, safeguarding them from degradation and extending their circulation time, thus improving their transport across the BBB [13]. Additionally, nanoparticles can be tailored to target specific receptors or transport mechanisms expressed on the surface of brain endothelial cells, facilitating their entry into the brain tissue. By encapsulating AEDs within nanoparticles and incorporating brain-targeting ligands or surface modifications, it becomes feasible to enhance drug delivery to the brain while minimizing systemic exposure and adverse effects.

In summary, brain-targeted drug delivery holds significant potential for enhancing the management of epilepsy by surmounting the challenges linked to delivering AEDs to the brain. By bolstering the delivery

of AEDs across the BBB and directing them precisely to the brain's site of action, brain-targeted drug delivery systems have the capacity to enhance therapeutic outcomes, decrease drug doses and dosing frequencies, and mitigate adverse effects, ultimately elevating the quality of life for individuals grappling with epilepsy. Continued research and innovation in this realm are indispensable for propelling the advancement of effective brain-targeted drug delivery strategies for epilepsy and other neurological disorders [14].

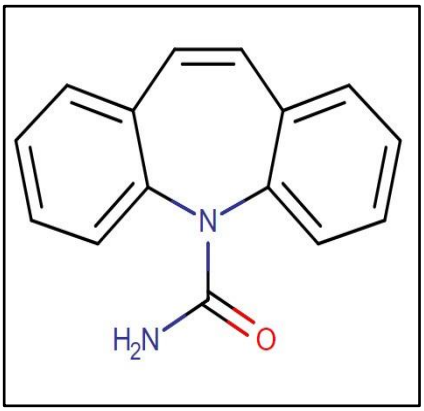
CARBAMAZEPINE

Carbamazepine, belonging to the dibenzazepine class, is a widely utilized antiepileptic and mood-stabilizing drug with a substantial clinical history. Originally developed in the 1950s, carbamazepine was primarily designated for treating trigeminal neuralgia, a severe neuropathic pain condition affecting the trigeminal nerve. However, its antiepileptic properties were swiftly acknowledged, leading to its widespread adoption for epilepsy management. The mechanism of carbamazepine involves the inhibition of voltage-gated sodium channels in neurons, which curtails the repetitive firing of action potentials, thereby diminishing neuronal excitability [15]. This mechanism aids in thwarting the abnormal electrical activity in the brain that underlies epileptic seizures and stabilizes mood in individuals grappling with bipolar disorder.

Beyond its efficacy in epilepsy and bipolar disorder, carbamazepine has exhibited effectiveness in a diverse array of other neurological and psychiatric ailments. It is frequently employed off-label to address conditions like neuropathic pain—comprising diabetic neuropathy and postherpetic neuralgia—as well as certain psychiatric disorders such as schizophrenia and borderline personality disorder. Furthermore, carbamazepine has found utility in managing substance use disorders, particularly in addressing alcohol withdrawal and cocaine dependence. Its wide-ranging spectrum of activity, coupled with its relatively favourable safety profile and cost-effectiveness, has firmly established carbamazepine as a versatile and indispensable medication in the therapeutic toolkit for neurological and psychiatric disorders [16].

Chemical Structure

Carbamazepine possesses a chemical configuration characterized by a tricyclic compound featuring a core structure of dibenzazepine, comprising a five-membered ring fused to a seven-membered ring. It is represented by the chemical formula C15H12N2O, with a molecular weight of around 236.27 g/mol.



Source: https://go.drugbank.com/drugs/DB00564

Importance

1. Antiepileptic Effects: Carbamazepine serves as a primary therapy for epilepsy, especially for focal seizures and generalized tonic-clonic seizures. Its mechanism involves stabilizing neuronal membranes and diminishing abnormal brain electrical activity to prevent seizures.

2. Mood Regulation: Beyond its antiepileptic role, carbamazepine acts as a mood stabilizer for bipolar disorder. It assists in managing manic and depressive episodes while steadying mood swings.

3. Trigeminal Neuralgia Management: Carbamazepine effectively treats trigeminal neuralgia, a persistent pain condition impacting the trigeminal nerve, by reducing the transmission of pain signals within the nervous system [17].

Properties

1. Mechanism of Action [18]

Carbamazepine primarily functions by obstructing voltage-gated sodium channels within neurons. This inhibition curtails the repetitive discharge of action potentials, thereby diminishing neuronal excitability. Such action aids in forestalling the abnormal synchronization of neuronal firing that underpins epileptic seizures and other neurological maladies.

2. Pharmacokinetics

When administered orally, carbamazepine is adequately absorbed, with peak plasma concentrations typically attained within 4 to 24 hours post-administration. It undergoes extensive hepatic metabolism, primarily mediated by the cytochrome P450 enzyme system, and its metabolites are excreted through urine. The elimination half-life of carbamazepine typically ranges from 10 to 20 hours, though it may be shorter in certain individuals.

3. Adverse Effects

Common adverse effects associated with carbamazepine include dizziness, drowsiness, nausea, vomiting, and rash. More severe reactions such as agranulocytosis, aplastic anemia, hyponatremia, and hepatic toxicity may also occur. Close monitoring for signs of adverse effects is essential for patients using carbamazepine, and any unusual symptoms should be promptly reported to a healthcare professional.

4. Drug Interactions

Carbamazepine engenders numerous drug interactions owing to its induction of cytochrome P450 enzymes, which can alter the metabolism of other drugs. It may diminish the efficacy of hormonal contraceptives, antidepressants, antipsychotics, and anticoagulants, among other medications.

REVIEW OF LITERATURE

1. Yadav KS and Satpute P (2019) reviewed recent progress in using starch nanoparticles (SNPs) for drug delivery. It describes different methods for synthesizing SNPs, such as high-pressure homogenization and ionic gelation, and the characteristics of the resulting nanoparticles. The article examines the stability, encapsulation efficiency, and release patterns of SNPs, along with their use in controlled and targeted drug delivery. The review highlights SNPs' ability to deliver various types of drugs, including hydrophobic ones, showcasing their versatility in drug delivery applications [19].
2. Perioli L et al., (2019) investigated the use of starch nanoparticles (SNPs) for drug delivery, emphasizing their compatibility with biological systems and adaptability. The study outlines synthesis techniques such as high-energy milling and solvent evaporation and evaluates SNPs' ability to load and release drugs. They concluded that SNPs offer a promising platform for delivering different types of drugs, including hydrophobic and biologically active molecules [20].
3. Vazquez-Ramos E et al., (2019) gave an overview of starch-based nanoparticles (SNPs) for drug delivery, including their potential use in targeting the brain. The article discusses the synthesis methods, surface modifications, and encapsulation techniques of SNPs relevant to drug delivery. The general principles covered herewith, such as controlled release and targeting abilities, also apply to brain-targeted delivery [21].
4. Van Gaalen J et al., (2019) analyzed the use of carbamazepine for treating focal epilepsy, particularly focusing on its efficacy and safety. The article provided an updated review of clinical research and real-world data on the use of carbamazepine in managing focal seizures. Major key points of the article include carbamazepine's effectiveness in decreasing seizure frequency and the necessity of vigilant monitoring for possible side effects [22].
5. Yuan M et al., (2019) investigated the potential interaction between carbamazepine and ibrutinib, a drug used to treat cancer. They evaluated how carbamazepine affects ibrutinib's pharmacokinetics and discussed the clinical consequences of taking the two drugs together. The findings emphasized the necessity for caution when combining carbamazepine with other drugs, especially those with narrow therapeutic ranges [23].
6. Sreeharsha N et al., (2018) examined biopolymer-based nanoparticles, including starch nanoparticles (SNPs), and their uses in drug delivery. The study emphasizes the advantages of biopolymer nanoparticles, such as their natural origin, biodegradability, and minimal toxicity. It discusses various applications, including targeted drug delivery and controlled release systems, aiming to enhance drug effectiveness and safety [24].
7. Berkovic SF et al., (2018) discussed the progress in understanding the genetics of epilepsy and how genetic mutations play a role in the disorder. The article highlights the potential of genetic

research to discover new therapeutic targets and enhance diagnostic accuracy. It also covers how genetics contribute to the development of personalized medicine and targeted treatments for epilepsy [25].

8. Zhang H et al., (2018) concentrated on using biopolymer nanoparticles, such as starch nanoparticles, for brain drug delivery. The article explores different elements of brain drug delivery, including targeting methods, controlled release, and surmounting the blood-brain barrier. It offered insights into how biopolymer nanoparticles can be designed for enhanced efficacy and safety in delivering drugs to the brain [26].
9. Tzellos TG et al., (2018) assessed the safety profiles of carbamazepine, oxcarbazepine, and eslicarbazepine acetate in treating epilepsy and bipolar disorder. The article discusses potential side effects, drug interactions, and safety concerns related to these antiepileptic drugs. The review explains the importance of tailoring therapy to individual patient needs and monitoring for possible adverse effects [27].
10. Kim et al., (2017) explored the synthesis and assessment of starch nanoparticles (SNPs) for drug delivery uses. The study covers methods like nanoprecipitation to produce SNPs and examines their physicochemical characteristics. The article delves into the encapsulation efficiency and drug release patterns of SNPs, highlighting their potential for controlled release systems. It also evaluates the biocompatibility of SNPs, which is essential for their use in pharmaceutical applications [28].
11. Tang, X et al., (2017) studied the preparation of starch nanoparticles (SNPs) for the controlled release of hydrophobic drugs. The article explains the encapsulation efficiency, release dynamics, and stability of SNPs, which are essential factors for delivering drugs to the brain [29].
12. French JA (2016) gave an overview of refractory epilepsy, a form of epilepsy that does not respond effectively to typical treatments. The study discusses the challenges of managing refractory epilepsy and the need for personalized treatment plans. It examines treatment options such as newer anticonvulsant drugs, surgery, and neurostimulation. The article stresses the importance of identifying the specific type of refractory epilepsy to customize treatment and the potential advantages of targeted therapies [30].
13. Brodie MJ et al., (2016) explored the importance of the MOA of antiepileptic drugs (AEDs) in their effectiveness for treating epilepsy. It discusses various classes of AEDs and their mechanisms, analyzing how these influence treatment results. The article emphasizes that knowledge of the mechanism of action can help in the selection of AEDs, particularly when certain mechanisms correlate with specific types of epilepsy [31].
14. Kwon EJ & Skalak MC (2016) outlined the principles and challenges of nanoparticle-based drug delivery for cancer treatment. The article discusses design factors for nanoparticles and promising

methods to enhance their effectiveness and safety. It addresses obstacles such as immune response, unawanted effects, and scalability issues, as well as potential solutions [32].

15. Ghanbarzadeh S et al., (2015) investigated the creation of starch nanoparticles and assessed their potential as a drug delivery system. The study centers on the synthesis and characterization of SNPs, including aspects such as particle size, shape, and drug encapsulation efficiency. Their work on the preparation and evaluation of SNPs as a drug delivery system provides essential insights applicable to brain delivery [33].
16. Kleefstra T et al., (2015) explored possible synergistic combinations of anticonvulsants, including carbamazepine, for managing seizures. They examined potential mechanisms and drug interactions that could enhance treatment outcomes and improve seizure control. The study suggested that certain combinations of anticonvulsants may offer benefits compared to monotherapy, while also stressing the need to monitor for adverse effects [34].
17. Zhang L & Gu FX (2015) investigated the transformative potential of nanomedicine, especially in cancer treatment. They examined different nanoparticle platforms and their capacity to improve drug delivery efficiency and specificity. The study underscored nanomedicine's influence on cancer therapy and the potential to develop more effective and safer treatments using various types of nanoparticles [35].
18. Sinha R et al., (2014) explored the potential use of starch nanoparticles (SNPs) for drug delivery, highlighting their adaptability. The study covers various techniques for creating SNPs, including nanoprecipitation and emulsification. It also details how SNPs can be modified on their surfaces to enable targeted and controlled drug delivery, as well as their compatibility with different types of drugs. The study concludes that SNPs offer benefits in terms of biocompatibility, biodegradability, and low toxicity, making them well-suited as carriers for drug delivery [36].
19. Loscher W et al., (2013) examined the ongoing quest for new epilepsy drugs and stressed the necessity for novel antiepileptic medications. The article outlines the limitations of current AEDs, such as side effects, drug interactions, and lack of efficacy in certain patients. It also discusses the potential advantages of developing new drugs that target unique pathways and mechanisms in epilepsy [37].
20. Beghi E et al., (2013) concentrated solely on carbamazepine and offered guidelines for the safe discontinuation of antiepileptic drugs, including carbamazepine. The article covered strategies for gradually tapering off carbamazepine and other antiepileptic drugs to minimize the risk of seizure recurrence. It highlighted the importance of personalized plans for drug withdrawal and close patient monitoring [38].
21. Loscher W & Brandt C (2010) reviewed the preclinical neurobiology of genetic generalized epilepsies from a translational perspective. The article discusses potential drug targets and

challenges in creating new anticonvulsants based on preclinical research. It emphasizes the complexities of translating animal models of epilepsy into successful clinical treatments [39].

22. Letchford K et al., (2009) explored polymeric micelles and nanoparticles for drug delivery to the central nervous system (CNS). They reviewed the difficulties of CNS drug delivery, including the challenge of the blood-brain barrier, and discussed how nanoparticles, including those based on starch, can help overcome these obstacles. The article also outlined strategies such as surface modification and targeting ligands to enhance brain-focused delivery and improve therapeutic results [40].
23. Farokhzad OC & Langer R (2009) highlighted the significant impact of nanotechnology on drug delivery, particularly in the realm of targeted delivery systems. It emphasizes nanotechnology's potential to revolutionize drug delivery and enhance therapeutic results across different medical areas. It also explores future challenges and directions for research and development in the field of nanotechnology-based drug delivery [41].
24. Wong HL et al., (2008) discussed the use of lipid-based nanoparticles for cancer therapy, including liposomes and solid lipid nanoparticles. The authors explore the advantages of these systems, such as improving drug solubility, stability, and targeted delivery. It also discusses applications and future possibilities for using lipid-based nanoparticles in cancer treatment [42].
25. Peer D et al., (2007) highlighted the use of nanocarriers as a promising approach for delivering drugs to cancer cells. The article discusses various types of nanoparticles, including liposomes, dendrimers, and polymeric nanoparticles. The study emphasizes the benefits of targeted drug delivery for better therapeutic results and decreased side effects in cancer treatment [43].
26. Kwan P & Brodie MJ (2006) emphasized the importance of promptly identifying refractory epilepsy to offer timely and effective treatment. The article discusses strategies for early intervention, such as quickly switching to alternative AEDs or considering surgical options. The article stresses the need for swift and precise diagnosis to guide treatment decisions and improve outcomes for patients with refractory epilepsy [44]

OBJECTIVES

1. Identify the ideal formulation parameters to produce starch nanoparticles specialized for targeting the brain effectively.
2. Achieve the maximum possible carbamazepine encapsulation efficiency in starch nanoparticles.
3. Analyse the physicochemical characterization of the carbamazepine-loaded starch nanoparticles, encompassing size, morphology, and drug release kinetics.
4. Examine the capacity of the nanoparticles to precisely target the brain tissues and managing the blood-brain barrier.
5. Evaluate the pharmacokinetic and pharmacodynamic profile of the carbamazepine-loaded starch nanoparticles in animal models.

PLAN OF WORK

1. Introduction

- Describe epilepsy as a neurological disorder characterized by recurrent seizures and problems with conventional anticonvulsant therapy.
- Emphasize the necessity for enhanced drug delivery systems to improve the effectiveness and minimize the adverse effects of anticonvulsant medications.
- Specify the objective to create brain-targeted starch nanoparticles containing an anticonvulsant agent for optimized drug delivery to the brain.

2. Objective

- Produce starch nanoparticles employing various techniques (hydrolysis-precipitation or ultrasonication) and analyse their physicochemical characteristics.
- Incorporate an anticonvulsant agent (e.g., carbamazepine) into the starch nanoparticles and refine the formulation parameters.
- Assess the brain-targeting effectiveness of the developed nanoparticles using in vitro blood-brain barrier models.

3. Review of Literature

- Give a brief overview of epilepsy, its underlying causes, and the available treatments, which include anticonvulsant drugs.
- Discuss the shortcomings of traditional anticonvulsant therapy, including poor brain penetration, systemic side effects, and inefficacy in some patients.
- Examine current developments in drug delivery systems powered by nanotechnology to improve the treatment of neurological disorders, with a focus on methods that target the brain.
- Examine the viability of using starch nanoparticles as delivery systems for medications to the brain, highlighting their flexibility, biocompatibility, and blood-brain barrier-crossing capabilities.

4. Methodology

- Starch Nanoparticle Production (hydrolysis-precipitation or ultrasonication)
- Incorporation of Anticonvulsant Agent (Drug- Carbamazepine)
- Physicochemical Characterization of Developed Nanoparticles
- Evaluation Using In Vitro Blood-Brain Barrier Models
- Assessment of Formulated Nanoparticles Effectiveness and Safety

5. Result & Discussion

- Analyse the outcomes of nanoparticle characterization, examining how synthesis parameters impact nanoparticle attributes and their significance for drug delivery.
- Review the results concerning the brain-targeting efficacy of the developed nanoparticles in vitro, detailing the mechanism of nanoparticle transport through the blood-brain barrier and factors affecting the cellular uptake.
- Evaluate the results of in vivo studies regarding the formulation's safety profile, potential neuroprotective qualities, and effectiveness in managing epilepsy.

6. Conclusion

- Outline the proposed study and its potential to advance drug delivery methodologies for treating epilepsy.
- Highlight the study's importance in meeting clinical demands and enhancing the quality of life for patients.

7. References

- Provide appropriate references to back up the planned research's justification, methodology, and expected outcomes.

METHODOLOGY.

1. **Drug and Starch:**

   Purchase:

   Purchase of drug that meet pharmaceutical-grade standards for anticonvulsant properties and starch that is suitable for use in nanoparticle mixtures.

   Fourier Transform Infrared Spectroscopy (FTIR):

   - Sample Preparation: Grind the drug and starch samples into a powder and make KBr pellets ready for FTIR examination
   - Instrumentation: Use a FTIR spectrometer set up correctly (for example, with the right resolution and wavelength range).
   - Analysis: Record spectra and examine peaks related to functional groups (e.g., -OH, C=O, C-H).

   Ultraviolet-Visible (UV-Vis) Spectroscopy of Drug and Starch:

   - Calculate the absorbance property of drug and starch samples in UV range.
   - Sample Preparation: Prepare drug and starch solutions in suitable solvents prepare the drug and starch solution.
   - Instrumentation: Use UV-Vis spectrophotometer set to the correct wavelength range (for instance, 200-800 nm).
   - Analysis: Evaluate the absorbance spectra and determine the concentrations by applying calibration curves.

2. **Synthesis of Starch Nanoparticles**
   - Utilization of techniques such as nanoprecipitation or ultrasonication to synthesize starch nanoparticles. Characterization of nanoparticles for particle size analysis and surface morphology using different techniques such as dynamic light scattering (DLS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM).
3. **Characterization of Nanoparticles**
   - Analyse physicochemical properties of the carbamazepine-loaded starch nanoparticles, including size distribution, zeta potential, and drug release profile.
   - Assess stability and drug release kinetics under physiological conditions.
4. **Loading of Drug into Starch Nanoparticles**
   - Conversion of anticonvulsant medication into starch nanoparticles for targeted delivery
   - Nanoparticle Formulation:
   - Employ methods like solvent displacement or emulsification to create nanoparticles.

- Adjust the parameters of the formulation (for example, the amount of medication to starch, concentration of surfactant).

5. **In Vitro Evaluation**
   - Evaluate BBB permeability using in vitro models.
   - Measure cellular uptake and intracellular localization of nanoparticles.
6. **In Vivo Evaluation**
   - Conduct pharmacokinetic studies in animal models (e.g., rats or mice) to determine the distribution and elimination of carbamazepine-loaded starch nanoparticles.
   - Evaluate brain targeting efficiency by measuring drug concentrations in brain tissue compared to other organs.
7. **Statistical Analysis**
   - Analyze data using appropriate statistical methods (e.g., ANOVA, t-tests) to compare different formulations and experimental conditions.
   - Ensure robustness and reproducibility of results.

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